7. Mahajan SK, Prasad AS, Lambujon J, et al: Improvement of uremic hypogeusia by zinc. Trans Am Soc Artif Intern Organs 1979; 25:443-448
8. McClain CJ, Kasarskis EJ, Allen JJ: Functional consequences of zinc deficiency. Prog Food Nutr Sci 1985; 9:185-226
9. Prasad AS: Clinical manifestations of zinc deficiency. Annu Rev Nutr 1985; 5:341-363
10. Tasman-Jones C: Zinc deficiency states. Adv Intern Med 1980; 26:97-114
11. Catalanotto FA: The trace metal zinc and taste. Am J Clin Nutr 1978; 31:1098-1103
12. Henkin RI, Schechter PJ, Hoye R, et al: Idiopathic hypogeusia with dysgeusia, hyposmia, and dysosmia—A new syndrome. JAMA 1971; 217:434-440
13. Catalanotto FA, Nanda R: The effects of feeding a zinc-deficient diet on taste activity and tongue epithelium in rats. J Oral Pathol 1977; 6:211-220
14. Solomons NW: Competitive interaction of iron and zinc in the diet: Consequences for human nutrition. J Nutr 1986; 116:927-935
15. Fawaz F: Zinc deficiency in surgical patients: A clinical study. JPEN J Parenter Enteral Nutr 1985; 9:364-369
16. Gordon EF, Gordon RC, Passal DB: Zinc metabolism: Basic, clinical, and behavioral aspects. J Pediatr 1981; 99:341-349

Penicillin-Induced Agranulocytosis

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SYSTEMIC PENICILLIN THERAPY is generally the treatment of choice in patients with bacterial endocarditis. Prolonged therapy at a high dosage is often required. Complications of treatment with penicillin, although uncommon, include hypersensitivity reactions ranging from mild urticaria to life-threatening anaphylaxis, central nervous system disorders, electrolyte disturbances, and acute interstitial nephritis. Hematologic complications of hypersensitivity to penicillin are rare. Coombs' test-positive hemolytic anemia has been reported.[1,2] Leukopenia also occurs, with 26 cases being reported to date. Agranulocytosis, however, has been previously reported only once, in 1946.[3] Herein we report a second case of agranulocytosis as a complication of penicillin therapy.

Report of a Case

The patient, a 17-year-old woman, presented with a three-week history of nocturnal fever not associated with rigors or chills. She had had generalized myalgia for two weeks and a generalized maculopapular rash for one week. Her family physician recorded a mitral regurgitant murmur and referred her to our hospital. There was no history of rheumatic fever, and her last dental visit was three months before the symptoms began.

On physical examination on admission she had a grade III/VI pansystolic murmur at the apex and a maculopapular rash over her extremities, but the results were otherwise normal. A chest x-ray film and an electrocardiogram were normal. Two-dimensional echocardiograms showed mitral valve prolapse with no valvular vegetations.

A clinical diagnosis of infective endocarditis was made and confirmed by identifying viridans group streptococci in each of nine blood cultures. The organism was sensitive to penicillin in vitro. Laboratory findings included the following: hemoglobin, 134 grams per liter; leukocyte count, 16.9×10^9 per liter, with 62% neutrophils and 24% lymphocytes. The urea, creatinine, electrolytes, plasma proteins, and liver enzyme levels were normal.

The intravenous administration of penicillin G sodium, 3 million units every six hours, and streptomycin sulfate, 100 mg given intramuscularly daily, was begun. Five days after starting treatment the patient was asymptomatic. On day 17 of her hospital stay, the streptomycin therapy was discontinued. The patient continued to do well until day 23, when she complained of a sore throat. Her leukocyte count was 3.2×10^9 per liter. Neutrophils were absent; the nucleated cells were predominantly atypical lymphocytes. Her hemoglobin was 130 grams per liter and the platelet count 332×10^9 per liter. A Coombs' test and assays for hepatitis B-associated antigen, heterophile antibody, antinuclear antibody, and rheumatoid factor were all negative. Serum immunoelectrophoresis showed an increase in polyclonal immunoglobulin (Ig) M and IgG. C3, C4, and CH_{50} assays were all negative.

A bone marrow aspirate showed normal cellularity with normal erythropoiesis. The myeloid:erythroid ratio was 3:1. Granulopoiesis showed no maturation beyond the promyelocyte stage.

Treatment with penicillin was discontinued on day 25, and a regimen of vancomycin hydrochloride was started. Two days later a peripheral blood monocytosis arose, accompanied by the appearance of bands. By day 30 the leukocyte count had risen to 17×10^9 per liter, with 0.48 neutrophils, 0.15 bands, 0.29 lymphocytes, and 0.08 monocytes. On discharge from hospital on day 34, there was no clinical evidence of the original infection.

Discussion

Leukopenia due to penicillin therapy is a rare event; only 26 cases—including this one—have been reported to date. We believe this to be the second report of penicillin-induced agranulocytosis in the past 50 years. In each case of penicillin-associated leukopenia, the patients received high-dosage penicillin for serious systemic infections. In 18 of 26 cases, therapy was for endocarditis. Table 1 summarizes the cases reported to date. All patients received their drugs by the intravenous or intramuscular routes. The earliest that leukopenia was noted was after four days of therapy, although it was seen as late as 35 days after penicillin treatment in one patient. The average duration of therapy before leukopenia occurred was 20 days. The range of total leukocyte counts at the nadir of the leukopenia was 0.1 to 3.9×10^9 per liter. Including our case, the absolute granulocyte count ranged from 0 to 1.998×10^9 per liter. The average granulocyte count was 0.372×10^9 per liter. In keeping with other reports, the total dose at the start of leukopenia was greater than 150,000 units per kg body weight per day.[4] All patients had normal leukocyte counts within 2 to 14 days of discontinuing the antibiotic therapy. The average time to recovery was 4.7 days. There were no deaths or permanent sequelae related to the leukopenia. Five patients had Coombs' test-positive hemolytic anemia.[1,2,5-7]

Bone marrow aspiration was done in 16 cases. The results of the aspirations showed no consistent pattern. Hypercellular, normocellular, and hypocellular marrows have been reported, although a hypocellular marrow was found in only one case.[11] In this case of gonococcal endocarditis, there appeared to be no features distinguishing it from cases associated with hypercellular and normocellular marrows.

Our case is consistent with other reports in total penicillin

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dose, duration of treatment, and duration of leukopenia. While it is possible that the leukopenia may have resulted from sepsis alone, it is more likely that the common factor was high doses of parenteral penicillin. The mechanisms of penicillin-induced leukopenia are as yet not fully understood. At least two distinct mechanisms of drug-induced leukopenia are known,[6,17] and both immunologic (type I) and toxic (type II) factors have been implicated. Antineutrophil antibodies have been detected in seven patients,[5,6,15,16] and circulating antipenicillin antibodies have been described as well.[2,6,18] Moreover, in a case described by Rossiter and co-workers, there was a previous history of penicillin-induced leukopenia.[5] Similarly, in the case described by Petz and Fudenberg, the readministration of penicillin resulted in a recurrence of Coombs' test-positive hemolytic anemia with leukopenia.[2] Interestingly, the initial hemolytic anemia with

TABLE 1.—*Summary of 26 Cases of Penicillin-Induced Leukopenia Reported*

Case	Source	Diagnosis	Age, yr	Sex	Penicillin Dose/d, million units	Days to Onset of Leukopenia	Cell Counts at Nadir WBC	PMN	%	Days to Recovery	Anti-leukocyte Antibody	Coombs' Test	Bone Marrow
							× 10^9/liter						
1	Spain and Clark, 1946[3]	Bowel obstruction	54	♂	100,000 U × 1d 160,000 U × 3d	4	0.10	0.00	0	1	...	...	Normal at autopsy
2*	Petz and Fudenberg, 1966[2]	Infective endocarditis	45	♂	100 IV	23	1.60	0.18	11	7	...	Pos	Normal cellularity; decreased granulocyte precursors
3	Forshaw, 1968[8]	Infective endocarditis	47	♂	8 IV × 14d 16 IV × 6d 32 IV × 13d	27	0.95	0.02	2	14	...	Neg	Increased cellularity; no mature granulocytes
4†	Rossiter et al, 1968[5]	Infective endocarditis	37	♂	Phenethicillin, 4 grams PO × 14d, then IM	28	0.80	0.03	4	3	Pos	Pos	Normal erythropoiesis; no mature granulocytes
5	White et al, 1968[1]	Infective endocarditis	64	♀	20 IV	18	3.20	...	...	2	...	Pos	Increased erythropoiesis, left-shifted granulopoiesis
6	Joorabchi and Kohout, 1973[7]	Infective endocarditis	12	♂	20 IV	18	2.30	0.16	7	14	...	Pos	Hypercellular, M:E 3:1, shift toward mature cells
7	Colvin et al, 1974[9]	Infective endocarditis	39	♀	20 IV × 7d 12 IV × 14d	23	0.90	0.08	9	5	Neg	Neg	Hypercellular; increased granulopoiesis
8	Homayouni et al, 1979[4]	Cellulitis	60	♂	230,000 U/kg IV	13	3.70	1.99	54	6	...	...	...
9		Gangrenous appendix	81	♂	250,000 U/kg IV	9	3.70	1.81	49	2	...	...	...
10‡	Neftel et al, 1981[6]	Infective endocarditis	54	♀	12 IV × 18d 32 IV × 3d	20	0.80	0.04	2	2	...	...	...
11‡		Infective endocarditis	28	♂	24 IV	19	2.00	0.10	5	4	Pos	Pos	...
12‡		Infective endocarditis	27	♂	16 IV	21	2.20	0.23	10	2	...	...	Hypocellular; maturation arrest, promyelocyte stage
13‡		Infective endocarditis	39	♂	20 IV	26	2.20	...	...	6	...	...	...
14‡		Infective endocarditis	25	♂	20 IV	24	1.80	...	...	3	Pos	...	Hyperactive marrow
15‡		Pneumonia	35	♂	16 IV	26	3.90	...	...	4	Pos	...	Maturation arrest, myelocyte stage
16		Hemangioma	13	♂	12 IV	19	3.40	...	...	10	Pos	...	Maturation arrest, myelocyte stage
17‡		Septic arthritis	64	♀	20 IV	26	2.50	1.00	40	3	...	...	...
18	Postelnick and Gaskins, 1981[10]	Infective endocarditis	21	♀	16 IV × 14d 20 IV × 3d	15	1.80	0.09	5	2	...	...	...
19§	Timmis et al, 1981[11]	Infective endocarditis	18	♀	20 IV	14	2.60	0.21	8	7	...	...	Hypoplastic
20	Yap, 1981[12]	Infective endocarditis	32	♂	16 IV × 7d 8 IV × 18d	25	1.20	0.21	17	3	...	Neg	...
21	Corbett et al, 1982[13]	Infective endocarditis	28	♂	8 × 20d 13 × 1d	22	0.90	0.40	44	3	...	...	Hypercellular; left-shifted granulopoiesis
22		Infective endocarditis	55	♂	12	35	0.70	0.50	72	2	...	...	Maturation arrest of WBC series
23	Miro et al, 1983[14]	Pleural empyema	40	♂	12	24	3.10	0.31	10	4	...	...	...
24	Rouveix et al, 1983[15]	Infective endocarditis	46	♂	250,000 U/kg IV	25	2.40	0.02	1	4	Pos	...	...
25	Snavely et al, 1983[16]	Infective endocarditis	31	♂	6 IV × 15d 15 IV × 14d	29	2.20	0.06	3	5	Pos	Neg	Hypercellular; increased granulocyte series; paucity of mature forms
26	This report, 1988	Infective endocarditis	17	♀	12 IV	22	3.20	0.00	0	8	Neg	Neg	Maturation arrest, promyelocyte stage

IM=intramuscularly, IV=intravenously, M:E=myeloid:erythroid ratio, Neg=negative, PMN=polymorphonuclear leukocytes, PO=orally, Pos=positive, WBC=lymphocytes

*Leukopenia recurred with the readministration of penicillin.
†Patient had a previous episode of penicillin G-induced granulocytopenia.
‡Data extrapolated.
§Granulocytopenia recurred after cefuroxime sodium and gentamicin sulfate were given.

leukopenia developed in this patient despite the prophylactic administration of prednisone. In another case where no antibodies were detected, the readministration of a single dose of penicillin resulted in a striking drop in the neutrophil count within 24 hours.[7] Although Neftel and associates have described circulating antipenicillin IgG antibodies in all their patients given penicillin in cumulative doses greater than 200 million units,[6,18] leukopenia did not develop in all patients so sensitized. The degree of sensitization may be diminished if the drug is given as a freshly prepared bolus rather than by slow infusion.[18,19]

The reports of neutropenia with the readministration of penicillin and the presence of antipenicillin antibodies favor a type I or hypersensitivity-type reaction. If this postulate is correct, this leaves the question of why antineutrophil antibodies have not been detected more frequently. One possibility is that the antibodies are of low concentration and of high affinity. In this situation, the antibodies would be almost all cell-bound, hence the free, detectable amount in the circulation would be low. If penicillin degradation products are required as haptens for the neutrophils, these would not be detected if fresh penicillin were added to the in vitro assay.[14] The occurrence, however, of penicillin-associated neutropenia in the face of prednisone therapy[1] argues against an immune-mediated reaction.

Another possible mechanism is that of a toxic, dose-related suppression of bone marrow precursors. This mechanism would be independent of circulating antipenicillin or antineutrophil antibodies. The almost invariable association with the administration of high doses of the drug and the fact that the neutropenia seldom occurred before 14 days favor this concept. Alternatively, the high dose and delayed onset may be related to the minimum dose needed for sensitization to occur. Joorabchi and Kohout have postulated that the pancytopenia seen in their patient was due to the penicillin-induced blockade of the release of mature cells from the marrow.[7]

The variation of marrow findings in the reported cases is intriguing and could possibly be explained by variations in the time of marrow sampling. Early in a patient's course, the marrow may be hypoplastic or aplastic and devoid of granulocytes and normoblasts. During the earliest phase of marrow recovery, there may be a transient increase in small dense lymphocytes in the marrow, subsequently replaced by the earliest granulocyte precursors.[17] Later, during recovery, the marrow would be extremely hypercellular with intense mitotic activity. Thus, "maturation arrest"—in which differentiation of marrow cells is considered to halt at a specific developmental stage—may be related only to the phase of recovery of the regenerating marrow.

Leukopenia is a rare complication of systemic penicillin therapy. It almost invariably occurs in cases of prolonged high-dose therapy. Monitoring the leukocyte count regularly during therapy may avert the occurrence of absolute granulocytopenia by detecting leukopenia early. Withdrawing penicillin therapy has resulted in a rapid return to normal of the leukocyte count in all cases.

1. White JM, Brown DL, Hepner GW, et al: Penicillin-induced haemolytic anaemia. Br Med J 1968; 3:26-29
2. Petz LD, Fudenberg HH: Coombs-positive hemolytic anemia caused by penicillin administration. N Engl J Med 1966; 274:171-177
3. Spain DM, Clark TB: A case of agranulocytosis occurring during the course of penicillin therapy. Ann Intern Med 1946; 25:732-733
4. Homayouni H, Gross PA, Setia U, et al: Leukopenia due to penicillin and cephalosporin homologues. Arch Intern Med 1979; 139:827-828
5. Rossiter MA, Gray IR, Shinton NK: Penicillin-induced haemolytic anaemia. Br Med J 1968; 3:616-617
6. Neftel KA, Wälti M, Spengler H, et al: Neutropenia after penicillins: Toxic or immune-mediated? Klin Wochenschr 1981; 59:877-888
7. Joorabchi B, Kohout E: Apparent penicillin-induced arrest of mature bone marrow elements. Br Med J 1973; 2:26-27
8. Forshaw J: Penicillin-induced granulocytopenia. Br Med J 1968; 3:184
9. Colvin B, Rogers M, Layton C: Benzylpenicillin-induced leucopenia—Complication of treatment of bacterial endocarditis. Br Heart J 1974; 36:216-219
10. Postelnick M, Gaskins JD: Penicillin G-induced granulocytopenia. Drug Intell Clin Pharm 1981; 15:289
11. Timmis AD, Crofts MA, Metcalfe J, et al: Gonococcal endocarditis with penicillin-induced bone marrow hypoplasia—Role of echocardiography. JAMA 1981; 246:672-673
12. Yap PK: Severe leucopenia and fever due to benzylpenicillin—A rare complication of treatment with a common antibiotic. Singapore Med J 1981; 22:99-101
13. Corbett GM, Perry DJ, Shaw TRD: Penicillin-induced leukopenia (Letter). N Engl J Med 1982; 307:1642-1643
14. Miro JM, Gatell JM, Moreno A, et al: More on penicillin-induced leukopenia (Letter). N Engl J Med 1983; 308:901-902
15. Rouveix B, Lassoued K, Vittecoq D, et al: Neutropenia due to β-lactamine antibodies. Br Med J [Clin Res] 1983; 287:1832-1834
16. Snavely SR, Helzberg JH, Bodensteiner DC, et al: Profound neutropenia associated with benzylpenicillin. South Med J 1983; 76:1299-1302
17. Pisciotta AV: Immune and toxic mechanisms in drug-induced agranulocytosis. Semin Hematol 1973; 10:279-310
18. Neftel KA, Müller MR, Hauser SP, et al: More on penicillin-induced leukopenia (Letter). N Engl J Med 1983; 308:901
19. Neftel KA, Wälti M, Spengler H, et al: Effect of storage of penicillin-G solutions on sensitisation to penicillin-G after intravenous administration. Lancet 1982; 1:986-988

Midcycle Pneumothorax in a Patient With Catamenial Pneumothoraces

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CATAMENIAL PNEUMOTHORAX is a syndrome of recurrent pneumothoraces developing within 48 to 72 hours of the start of menstrual bleeding. In most cases they are small, unilateral, right-sided pneumothoraces occurring in parous women in their third and fourth decades. The close temporal relationship to menses has led several authors to conclude that evidence of pneumothorax at other times in the cycle precludes the diagnosis.[1-3] We report the case of a patient with catamenial pneumothorax in whom pneumothoraces developed between menses.

Report of a Case

The patient, a 39-year-old nonsmoking woman, presented for evaluation of recurrent pneumothoraces. She had been admitted to hospital twice with shortness of breath, cough, and chest pain. Chest radiographs showed small right-sided pneumothoraces without other abnormalities. During both hospital stays, therapy included only oxygen and analgesics. She recalled that each admission corresponded with the beginning of her menstrual period. In the following year the same symptoms recurred several times, always within 48 hours of the start of menstrual bleeding, but she saw her physician only when she needed analgesics. On each visit, a chest radiograph showed a small right-sided pneumothorax.

A year after her initial diagnosis, she also noticed shortness of breath, cough, and chest pain between menses. On day 14 of a menstrual cycle, she consulted her physician at the

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